Remarks

The Examiner is thanked for granting and participating in a telephone interview with one of the Applicants, Dr. Michael Underhill, and the undersigned on November 19, 2003 to discuss the various patentability issues and to suggest possible claim amendments to overcome the rejections presented by the Examiner in the final Office Action dated September 23, 2003 (the Final Action).

Claims 1-26, 30 and 31 are pending in the present application. Claims 16, 22 and 23 have been withdrawn from consideration. Claims 1-15, 17-21, 24-26, 30 and 31 stand rejected. Applicants have amended claims 1, 2, 5, 9, 12, 13, 14, 17, 18, 19, 20, 21, 24, 30 and 31 herein. Applicants have added new claims 32-34 which are supported by the specification. The concerns presented in the Final Action are discussed below.

Claim Rejections - 35 U.S.C. §103

A. Claims 1-15, 17-21 and 24-26 and 30 stand rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over WO 98/08646 (hereinafter "'646 reference"). The Applicants respectfully disagree with this assertion.

The Examiner alleges that the '646 reference discloses pharmaceutical compositions comprising an RAR antagonist and a pharmaceutically acceptable carrier for the treatment of disorders such as rheumatoid arthritis. Furthermore, the Examiner alleges that the reference teaches combining the composition with other drugs. Based on the Examiner's assertions of the teachings of the document, the Examiner alleges that it would have been obvious to one of ordinary skill in the art to devise pharmaceutical compositions and methods of treatment incorporating additional drugs or osteogenic factors for bone development.

Contrary to the Examiner's position, the '646 reference is directed to a composition containing a combination of an RAR antagonist and an RXR agonist for the treatment of cancer (i.e., cellular hypertrophy) and inflammatory disorders that include cancers, skin disorders and rheumatoid arthritis. As such, the reference teaches use of the composition for reducing **inflammation** associated with any inflammatory disorder such as rheumatoid arthritis. Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints.

It should be noted that rheumatoid arthritis can also cause inflammation of the tissue around the joints, as well as other organs in the body. Autoimmune diseases are illnesses which occur when the body tissues are mistakenly attacked by its own immune system. The immune system is a complex organization of cells and antibodies designed normally to "seek and destroy" invaders of the body, particularly infections. Patients with these diseases have antibodies in their blood which target their own body tissues, where they can be associated with inflammation. Because it can affect multiple other organs of the body, rheumatoid arthritis is referred to as a systemic illness and is sometimes called rheumatoid disease. The chronic inflammation associated with rheumatoid arthritis leads to the destruction of the cartilage, bone and ligaments causing deformity of the joints. Damage to the joints can occur early in the disease and be progressive. The '646 reference attempts to treat rheumatoid arthritis by the use of a composition containing a combination of RAR antagonist and RAR agonist to reduce the inflammation that may lead to the destruction of cartilage.

Claim 1 has been amended to clarify that the RAR antagonist composition comprises RAR antagonist(s), a pharmaceutical carrier and a chondrogenic stimulator. The '646 reference does not teach or contemplate the inclusion of a chondrogenic stimulator in any RAR antagonist composition. A chondrogenic stimulator is supported in the present specification at page 18, line 31. The '646 reference only recites on page 24 that "drugs" may be combined with the RAR antagonist and RXR agonist. "Drugs" **are not the same as** a "chondrogenic stimulator" nor would one of ordinary skill in the art come to the conclusion that reciting "drugs" would contemplate a "chondrogenic stimulator". Where the '646 reference is completely silent as to any teaching of cartilage or cartilage formation, it would not be obvious to one of ordinary skill in the art to use a chondrogenic stimulator when the reference is directed to inflammatory diseases. Furthermore, the '646 reference is silent as to an RAR antagonist composition for use in methods and devices for inducing chondrogenesis to repair any damaged cartilage. Applicants respectfully submit that it is only through impermissible hindsight by using the present inventors' discovery regarding the role of RAR antagonists in chondrogenesis and the use of a composition comprising (a) an RAR antagonist; (b) a pharmaceutically acceptable carrier; and (c) a chondrogenic stimulator, leading to cartilage formation or chondrogenesis leading to cartilage

formation that further mediates formation of new bone tissue in a vertebrate is one able to arrive at the present invention.

On page 3 of the Final Action, the Examiner alleges that it would be obvious from the teachings of the '646 reference to develop bones. It is noted that the present application **is not directed to the development of bones**. The claims are directed to the stimulation of chondrogenesis in those tissues and in conditions where such is desired.

Chondrogenesis involves the formation of chondroprogenitors from multipotential mesenchymal cells and their subsequent differentiation into chondroblasts and chondrocytes. This is reflected in the description of cartilage formation at page 26 of the present application (and page 21 of the priority application) as involving two steps: 1) condensation of mesenchymal cells; 2) differentiation of condensed mesenchyme to matrix producing chondrocytes. Articular cartilage is provided in joints to provide a low friction surface to allow mobility and acts to cushion the ends of bones. Cartilage production is therefore required and desired in joints where chondrocytes remain for the life as chondrocytes. In other tissues, cartilage formation is an intermediate step in the process of bone formation. Once chondrogenesis is over, chondrocytes go on to mature and undergo hypertrophy, followed by mineralization of the cartilage and its eventual replacement by bone. This occurs, for example, within the growth plate of developing humans and other mammals and allows for the growth of long bones. Overall, chondrogenesis is desired for the maintenance and repair of cartilage in joints as well as to provide sufficient mature cartilage that can be mineralized for the growth of long bones.

Claims 1, 9, 20 and 21 have been amended to recite "chondrogenesis leading to cartilage formation or chondrogenesis leading to cartilage formation that further mediates formation of new bone tissue". As such, the RAR compositions of the present invention are used **directly** to stimulate chondrogenesis which is not disclosed or suggested by the cited references.

To summarize, the '646 reference does not suggest or provide any motivation to provide a composition of RAR antagonist(s) and chondrogenic stimulator (claim 1) because the reference is directed to inflammatory conditions and not stimulation of

chondrogenesis. The '646 reference is also silent as to any method for inducing chondrogenesis (claim 9); or for providing a morphogenic device of an implantable carrier with an RAR antagonist dispersed therein (claim 12); or for promoting *in vivo* integration of an implantable device (claim 17); or for providing any type of method to promote chondrogenesis (claims 19-21, 24 and 30).

It is well-established case law that in order to establish a *prima facie* case of obviousness, the cited references must disclose all the claim recitations of the present invention, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to arrive at the claimed invention, and lastly, the cited references must provide a reasonable expectation of success. The '646 reference is completely silent with respect to that claimed in claims 1-15, 17-21, 24-26 and 30 and as such, does not render these claims obvious.

B. Claims 1-15, 17-21, 24-26 and 31 stand rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over U.S. Patent 6,184,256 to Basset et al. (Basset et al.). The Applicants respectfully disagree with this assertion.

Basset et al. is directed to methods for screening compositions for the purpose of differentially modulating the expression of mammalian genes comprising at least one AP1- binding site and at least one RARE. In one aspect, such an identified composition may comprise a mixture of at least one RXR agonist or RXR antagonist and optionally a RXR pan-antagonist. The compositions are used for the treatment of physical disorders that can be delayed, prevented or cured by modulating matrix metalloproteinase (MMP) gene expression such as cancers, inflammatory disorders such as rheumatoid arthritis, fibrotic disorders, osteoporosis and ocular disorders. Basset et al. describes administering the noted compositions in combination with other "drugs", however, such "drugs" are not further described.

Basset et al. is silent with respect to the use of a composition comprising an RAR antagonist, pharmaceutical carrier and chondrogenic stimulator for the stimulation of chondrogenesis. The discussion of inflammatory disorders such as rheumatoid arthritis is provided above. Osteoporosis is a bone condition characterized by a decrease in bone mass, resulting in bones that are more porous and more easily

fractured than normal bones. Fractures of the wrist, spine, and hip are most common; however, all bones can be affected. The most common form of the disease, primary osteoporosis, includes postmenopausal, or estrogen-deficient, osteoporosis (Type I), which is observed in women whose ovaries have ceased to produce the hormone estrogen; age-related osteoporosis (Type II), which affects those over the age of 70; and idiopathic osteoporosis, a rare disorder of unknown cause that affects premenopausal women and men who are middle-aged or younger. Secondary osteoporosis may be caused by bone disuse as a result of paralysis or other conditions, including weightlessness in space; endocrine and nutritional disorders, including anorexia nervosa; specific disease processes; and certain drug therapies. Prevention and treatment of osteoporosis include synthetic estrogen or progestin therapy or both for postmenopausal women, intake of calcium and other nutrients, weight-bearing exercise, and drugs such as calcitonin and alendronate sodium, a non-hormonal treatment for osteoporosis. From this description of osteoporosis and its current treatments, it is apparent that the stimulation of chondrogenesis to treat such conditions presents a novel treatment alternative.

Basset et al. does not suggest the claimed compositions, methods or implantable devices which are all directed to the stimulation of chondrogenesis. Basset et al. is silent and does not teach or suggest processes related to cartilage or stimulation of chondrogenesis. In fact, Basset et al. teaches away from the claimed invention because it is directed to modulating the expression of matrix metalloproteinase (MMP) genes.

C. Claims 2, 4 and 6 are rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over U.S. Patent 6,326,397 to Bollag et al. (Bollag et al.). Bollag et al. describes a specific retinoid antagonist compound for increasing the production of IL-12 and to suppress T helper cell type 2 activity, and thus, for therapy for immune disorders mediated by such activity, more specifically inflammatory disorders. This reference is silent as to the use of any of its disclosed antagonists in a composition with a pharmaceutically acceptable carrier and chondrogenic stimulator for the stimulation of chondrogenesis. The other "substances" noted by the Examiner in column 11, lines 20-22, are **not** agents considered to be a chondrogenic stimulator. Stimulating chondrogenesis is completely different from treating or reducing inflammation, with

the later not involving chondrogenesis. Thus, the teachings of Bollag et al. do not render these claims obvious.

The Examiner's comments on page 6 of the Final Action, first paragraph, are not relevant to the claimed invention. The claimed invention is directed to stimulating chondrogenesis and does not contemplate compositions or methods for bone formation. Again, claims 1, 9, 20 and 21 have been amended to recite "chondrogenesis leading to cartilage formation or chondrogenesis leading to cartilage formation that further mediates formation of new bone tissue". As such, the RAR compositions of the present invention are used directly to stimulate chondrogenesis and this process is not disclosed or suggested by the cited reference.

The Applicants further take this opportunity to address the Examiner's mischaracterization of the relationship between arthritis and chondrogenesis and osteoporosis and chondrogenesis on page 8 of the Final Action where it is stated that "arthritis and osteoporosis require chondrogenesis for treatment". There is no scientific support for this comment in any of the references cited by the Examiner. In fact, it is the present invention that provides compositions and methods of treatment for certain types of arthritis and cartilage defects in general by the stimulation of chondrogenesis. Brief descriptions of rheumatoid arthritis (an autoimmune disease) and osteoporosis are provided above. Furthermore, in the telephone interview granted on November 19, 2003 with the Examiner, the co-inventor Dr. Michael Underhill (who is certainly one skilled in the art in the field as is evidenced in the attached *curriculum vitae*) explained in great scientific detail the differences between chondrogenesis and osteogenesis. Dr. Michael Underhill also explained in great detail how each of the cited references were directed to reduction of inflammation in various clinical conditions which include rheumatoid arthritis. Based upon Dr. Michael Underhill's expertise, it was evident that chondrogenesis and osteogenesis are two separate entities and that the cited references do not describe events related to chondrogenesis.

In general, arthritis is any of more than 100 different diseases causing pain, stiffness, and in most cases, swelling in the joints. Joints are found where two bones in the body meet, cushion the bones and prevent them from rubbing against each other during movement. Joints are composed of cartilage—smooth, elastic tissue—

surrounded by a casing called the joint capsule. The joint capsule is lined with a synovial membrane that secretes synovial fluid, a liquid that fills the joint cavity and further reduces friction between the bones. Although all arthritic conditions involve joint pain, the severity, duration, and effects of this pain vary considerably from one condition to another. The most common form of arthritis is osteoarthritis (OA), also known as degenerative joint disease. In OA, the cartilage cushion in the joints breaks down, causing the bones to rub together. Pain, stiffness, and sometimes the formation of bone growths, called spurs, result. OA can affect any joint, but it is most common in the hands, feet, spine, and in large, weight-bearing joints such as the hips and knees. The most common form of treatment for OA is surgical intervention and pain management.

In summary, none of the cited references alone or in combination suggest the claimed compositions, devices or methods involving such compositions of RAR antagonist for stimulation of chondrogenesis or for the treatment of a variety of conditions such as cartilage defects and cartilage defects that may be caused by arthritis.

As previously stated, the case law is clear with respect to obviousness. In this instance, the cited references are completely silent as to any teaching relating to chondrogenesis. As such, one of ordinary skill in the art would not have been motivated by the cited references, or would have expected that the teachings of the cited references would lead one to chondrogenesis or have any effect on chondrogenesis as recited in the present claims. The cited references clearly fail to suggest the desirability of making the claimed invention. Lastly, the cited references fail to provide a reasonable expectation of success of arriving at the claimed invention.

Accordingly, the Applicants respectfully submit that claims 1-15, 17-21, 24-26, 30 and 31 are not obvious under 35 U.S.C. § 103(a) in view of the cited references, and respectfully request that this rejection be withdrawn.

Conclusion

In view of the foregoing amendments and remarks, the Applicants respectfully request that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. The Examiner is invited and encouraged to contact

the undersigned directly if such contact will expedite the prosecution of the pending claims to issue. In any event, any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

A check in the amount of $ 1,756.00 is enclosed. This amount is believed to be correct. However, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 50-0220.

Respectfully submitted,

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